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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/782,590

01/13/97

ROSE

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43/24

EXAMINER

HM22/0525

UNGAR, S

ART UNIT

PAPER NUMBER

1642

27

DATE MAILED:

05/25/00

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/782,590

Applicant(s)

Rose

Examiner

Ungar

Group Art Unit

1642



☒ Responsive to communication(s) filed on Nov 16, 1999

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-87 is/are pending in the application.

Of the above, claim(s) 1-68 and 84-87 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 69-83 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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1. The request filed on April 28, 1998 for a Continued Prosecution Application (CPA) under 37 CAR 1.53(d) based on parent Application No. 08/782,590 is acceptable and a CPA has been established. The Preliminary Amendment and Declarations (both the Epstein Declaration and the Rapport Declaration) filed on November 16, 1999 (Paper No. 25) are acknowledged and have been entered. An action on the CPA follows.
- 2 The Claims 69-83 are pending and currently under examination. Claims 1-68 and 84-87 remain withdrawn from consideration for the reasons previously set forth.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. The following objections are being maintained:

Objection to the specification in Paper No. 10, Section 3, page 4 for the reasons previously disclosed.

Applicant argues that pages 14-16 contain a description of each of the drawing of Figures 1-44. The argument has been noted but has not been found persuasive because a review of the specification revealed that there is not an adequate description of each drawing. For example, the drawings are replete with numbers (for example, see Figure 36) which are not defined or described in any way in the Brief Description of the Drawings.
5. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

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6. Claims 69-83 remain rejected under 35 USC 112, first paragraph essentially for the reasons disclosed in Paper No. 10, Section 5(a) pages 5-8 and Paper No. 15 Section 5, pages 2-5.

Applicant argues that (a) methods of making indoxyls as the soluble precipitable material are found on pages 20-23, making soluble precipitable material comprised of soluble and insoluble moiety on pages 23-24 and methods of radio labeling are found on page 23 and in Figs. 15-17 and methods and dosages of the bispecific reagent and the therapeutic agent are readily taught by the prior art of ADEPT, (b) it is widely known that immobilization of radio-isotopes can be used successfully for therapy, © it is clear that the therapeutic agent is not therapeutic *per se* when administered *in vivo* but only becomes therapeutic as disclosed in the specification when it is concentrated and retained in situ, (d) although ADEPT fails for reasons other than the administered dose of the prodrug because the active drug diffuses away from the site but in the present invention, the radio-isotope atoms are immobilized, (e) the therapeutic agent is not a protein and proteolytic degradation is not relevant and the therapeutic agent is a radio-labeled soluble precipitable material which circulates freely in all body fluids and is only converted to an insoluble material by non-mammalian enzymes bound to bispecific reagent and this is the only location where it will be immobilized and therefore retained for a long period of time, (f) claim 5 describes proteins and peptides, (g) insoluble materials do not diffuse, only soluble materials diffuse and the insoluble precipitate is not removed from the area because tumors lack effective lymphatic drainage and is not removed by phagocytic activity because macrophage and phagocytic activity in the tumor is

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reduced and Applicant admits on the record that ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues". The arguments have been noted but have not been found persuasive because (a') general methods of indoxyl chemistry, preparation of precipitable material and methods of radio labeling have been taught but the specification does not provide guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo* and Applicant admits on the record that the therapeutic agent is only therapeutic after conversion. Without working examples that demonstrate that the conversion takes place *in vivo* which would provide guidance to one skilled in the art, given the issues raised in Paper No. 10, one of skill in the art could not predict that the therapeutic agent taught could be used with a reasonable expectation of success, (b') applicant is arguing limitations not present in the claims as currently constituted as immobilization of a radioisotope is not claimed, (c') Applicant is claiming a therapeutic agent, not a method for conversion of a prodrug to a therapeutic agent. Applicant admits on the record that the claimed therapeutic agent is not therapeutic *per se*, (d') applicant is arguing limitations not recited in the claims as presently constituted as the claims are not drawn to immobilized radioisotope atoms, (e') it is clear that the limitation that the therapeutic agent is not a protein is not recited in the claims as presently constituted and further, other than claim 83, none of the claims are drawn to radio-labeled soluble precipitable material and none of the claims are drawn to immobilized reagents. Without working examples, in view of the issues raised in Paper No. 10, one of skill in the art could

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not predict that the only location where the therapeutic agent will be immobilized will be at the site of the bispecific reagent, (f') the issue raised here was not that the specification does not describe protein and peptides as candidates for the soluble precipitable material but that Applicant's response was confusing because Applicant stated on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material, (g') Applicant was invited to submit objective evidence to resolve this issue, no objective evidence has been submitted but Applicant has admitted on the record that "ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues".

Further, the Epstein Declaration specifically teaches how the instant invention is similar to ADEPT and how it is different than ADEPT. The Epstein Declaration further goes on to express the opinion that the disclosed invention has great therapeutic potential and can be easily made and tested. The argument has been considered but has not been found persuasive because Dr. Epstein specifically states that the invention has great potential and can be made and tested. It is clear that, in the absence of objective evidence, Dr. Epstein cannot predict that the therapeutic agent will function as claimed and for the reasons previously set forth, that it cannot be predicted, in the absence of *in vivo* working examples, that the claimed therapeutic agent will function as claimed. Finally, Dr. Epstein comments on Examiner's statement that "one of skill in the art would expect that an insoluble precipitate would be removed from the claimed region either by convection, diffusion or by phagocytosis. Dr. Epstein states that insoluble DNA is retained

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much longer in tumor tissue compared to normal tissue and that one skilled in the art would readily recognize that the insoluble precipitate formed in Dr. Rose's invention will be retained in the same way. The argument has been considered but has not been found persuasive because it is clear that, although retained longer, the insoluble precipitate will be removed. It cannot be determined or predicted from the information in the specification or in the art of record that the invention will function as claimed. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 69-83 remain rejected under 35 USC 112, first paragraph essentially for the reasons disclosed in Paper No. 10, Section 5(b) pages 8-10 and Paper No. 15 Section 6, pages 5-6.

Applicant argues (a) as in Sections 1(d), (b) the specification teaches how to make the soluble precipitable material cell impermeant. The arguments have been considered but have not been found persuasive for the reasons set forth above drawn to Section 1(d). Although the specification teaches how to make the soluble precipitable material cell impermeant, the specification does not teach how to use the therapeutic agent for the reasons set forth above.

The Rapaport Declaration states that "sufficient detail of invention is described in the specification" to enable one skilled in the art to make the various soluble precipitable materials described. The argument has been considered but has not been found persuasive because, as set forth above, the specification does not teach how to use the invention.

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Further, the Epstein Declaration states that “in view of the long standing and established field of ADEPT, the information providedenables one skilled in the art to practice the present invention” and that the “therapeutic protocols of the present invention disclose required doses of the therapeutic agent.....” which are borne out in the long-standing and well-established field of ADEPT. Dr. Epstein states that the Examiner speculates that the dosage and methods of administration used in the prior art would not be expected to enable the instant claims. Dr. Epstein emphatically states that this speculation is not supported by the Examiner since the prior art of ADEPT and the invention disclosed in the ‘590 application are different. The Argument has been considered but has not been found persuasive since Dr. Epstein clearly states that the instant invention and the ADEPT method are different and Examiner again reiterates that the methods used in ADEPT treatments are not enabling for the instant invention.. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claims 69-83 remain rejected under 35 USC 112, first paragraph essentially for the reasons disclosed in Paper No. 10, Sections 5(c) p. 10 and 5(d) p. 11 and Paper No. 15 Section 8, page 7.

Applicant argues that Declarations of Professor Rapoport and Dr. Epstein are drawn to the issue raised.

The Epstein Declaration reiterates the opinion that since ADEPT is known and since the instant invention overcomes problems known to be prevalent in ADEPT therapy, that the invention is enabled, especially in light of vast amounts of research in the ADEPT art and the fact that guidelines for doses have been well-

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established by research and publications for ADEPT. The Epstein argument has been noted but has not been found persuasive for the reasons set forth previously and above, that is that in the absence of objective evidence, in view of the known unpredictability of the cancer therapeutic arts, it could not be predicted that the claimed therapeutic agent would function as claimed. The Epstein Declaration further states that attachment of large and/or anionic molecules to a product will make that product impermeant. The argument has been considered but has not been found persuasive because the issue raised here is not that a molecule cannot be made impermeant, but rather that the specification does not teach how to use the claimed molecule so that it will function as claimed.

The Rapaport Declaration argues that is known how to attach molecules to the soluble precipitable materials to make them cell impermeant. The argument has been considered but has not been found persuasive because the issue raised here is not that a molecule cannot be made impermeant, but rather that the specification does not teach how to use the claimed molecule so that it will function as claimed.

Applicant's arguments have not been found persuasive and the rejection is maintained.

9. Claims 69-82 remain rejected under 35 USC 112, second paragraph essentially for the reasons disclosed in Paper No. 10, Section 6(e) and Paper No. 15 Section 9, page 7.

Applicant argues that the therapeutic agent is radioactive and therefore must cause some cell damage. The arguments have been considered but have not been found persuasive because applicant is arguing limitations not recited in the claims as

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presently constituted. Applicant's arguments have not been found persuasive and the rejection is maintained.

10. Claim 79 remains rejected under 35 USC 112, second paragraph essentially for the reasons disclosed in Paper No. 10, Section 6(s) and Paper No. 15 Section 9, page 8.

Applicant argues claim 79 has been amended to provide a better definition of the invention. The argument has been noted but has not been found persuasive because the amendment did not include the deletion of the indefinite term "derivatives". Applicant's arguments have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

11.. Claims 69-82 remain rejected under 35 USC 102 (b) essentially for the reasons disclosed in Paper No. 10, Section 8, pages 16-18 and Paper No. 15, Section 10, pages 8-9.

Applicant argues that the Epstein Declaration addresses the instant rejection. The Epstein Declaration states the opinion that the drugs recited in the cited reference are all soluble. The argument has been considered but has not been found persuasive. Applicant was invited to present objective evidence showing that all of the recited prodrugs, when converted into drugs were soluble. No subjective evidence has been submitted. Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

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12. Claims 71 and 72 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a "molecule" has no clear support in the specification and the claims as originally filed. A review of the specification discloses support for a "chemical" but no support for the broadly worded claim of a "molecule". The subject matter claimed in claims 71 and 72 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point to page and line number in the specification that provides support for the newly claimed limitation.

13. Claims 77-79 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a "reducing the ability of indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion and convective flow in the extracellular fluid" has no clear support in the specification and the claims as originally filed. The subject matter claimed in claims 77-79 broadens the scope of the invention as originally disclosed in the specification. Applicant is invited to point to page and line number in the specification that provides support for the newly claimed limitation.

14. Claims 69-83 are rejected under 35 USC 112, second paragraph as indefinite because claim 69 recites the phrase "a period of time". The phrase is a relative phrase and is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of "time" and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

15. All other objections and rejections recited in Paper No. 15 are withdrawn.

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16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.



Susan Ungar
Primary Examiner
May 22, 2000